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The association of nocturnal hypertension and nondipping blood pressure with treatment-resistant hypertension: The Jackson Heart Study

Marguerite R. Irvin PhD[1] | John N. Booth III PhD[1] | Mario Sims PhD[2] | Adam P. Bress PharmD[3] | Marwah Abdalla MD[4] | Daichi Shimbo MD[4] | David A. Calhoun MD[5] | Paul Muntner PhD[1]

[1]Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, Birmingham, AL, USA

[2]Department of Medicine, University of Mississippi Medical Center, Jackson, MS, USA

[3]Department of Population Health Sciences, University of Utah School of Medicine, Salt Lake City, UT, USA

[4]Department of Medicine, Columbia University Medical Center, Columbia University, New York, NY, USA

[5]Vascular Biology and Hypertension Program, Division of Cardiovascular Disease, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA

Correspondence
Marguerite R. Irvin, Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, Birmingham, AL, USA.
Email: irvinr@uab.edu

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Apparent treatment-resistant hypertension (aTRH), nocturnal hypertension, and nondipping blood pressure (BP) have shared risk factors. The authors studied the association between aTRH and nocturnal hypertension and aTRH and nondipping BP among 524 black Jackson Heart Study participants treated for hypertension. Nocturnal hypertension was defined by mean nighttime systolic BP ≥120 mm Hg or diastolic BP ≥70 mm Hg. Nondipping BP was defined by mean nighttime to daytime systolic BP ratio >0.90. aTRH was defined by mean clinic systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg with three medication classes or treatment with four or more classes. The risk for developing aTRH associated with nondipping BP and nocturnal hypertension was estimated. After multivariable adjustment, participants with aTRH were more likely to have nocturnal hypertension (prevalence ratio, 1.20; 95% confidence interval, 1.03–1.39) and nondipping (prevalence ratio, 1.25; 95% confidence interval, 1.09–1.43). Over a median 7.3 years of follow-up, nocturnal hypertension and nondipping BP at baseline were not associated with developing aTRH after adjustment.

1 | INTRODUCTION

Blacks are two times more likely than whites to have apparent treatment-resistant hypertension (aTRH), defined as clinic-measured systolic blood pressure (SBP) ≥ 40 mm Hg or diastolic blood pressure (DBP) ≥ 90 mm Hg despite the use of antihypertensive medications from three different classes or treatment with four or more classes regardless of blood pressure (BP) level.[1] The prevalence of nocturnal hypertension, defined as a mean nighttime SBP ≥ 20 mm Hg or DBP ≥ 70 mm Hg, and nondipping BP, defined as mean nighttime to daytime SBP ratio > 0.90 is also high among blacks.[2,3] Comorbidities including sleep apnea, chronic kidney disease, obesity, and diabetes mellitus are common in individuals with aTRH and are established risk factors for nocturnal hypertension and nondipping BP.[4,5] Therefore, we hypothesized that the prevalence of nocturnal hypertension and nondipping BP is higher among individuals with aTRH vs their counterparts with hypertension but not aTRH.

To test this hypothesis, we compared the prevalence of nocturnal hypertension and nondipping BP in a cohort of black patients with vs without aTRH. Additionally, prior studies have reported that nocturnal hypertension and nondipping BP are associated with an increased risk for developing hypertension based on BP measurements obtained

in the clinic.[6,7] However, few data are available on whether nocturnal hypertension and nondipping BP are associated with developing more difficult to control BP. In a secondary analysis, we determined the association between nocturnal hypertension and nondipping BP with the development of aTRH. We performed these analyses using both clinic-measured BP and ambulatory BP monitoring (ABPM) data from 524 participants taking antihypertensive medication from JHS (Jackson Heart Study), a community-based, prospective cohort study comprised exclusively of black individuals.[8]

2 | METHODS

2.1 | Study population

The JHS was designed to evaluate cardiovascular disease (CVD) risk among black individuals.[9] Briefly, JHS enrolled 5306 black persons, aged ≥21 years, between 2000 and 2004 from the ARIC (Atherosclerosis Risk in the Community) site in Jackson, Mississippi, and a representative sample of urban and rural Jackson, Mississippi, metropolitan tricounty (Hinds, Madison, and Rankin counties) residents, volunteers, randomly contacted individuals, and secondary family members of participants.[8] The current analysis was restricted to participants who underwent ABPM following the baseline examination (n = 1148) and met IDACO (International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (IDACO) criteria for a complete ABPM (n = 1046, defined below). Also, participants were required to have complete information on clinic-measured BP and antihypertensive medication use at the baseline examination (examination 1 in 2000–2004) and at least one follow-up examination (examination 2 in 2005–2008 and/or examination 3 in 2009–2013). As only people who are taking antihypertensive medication can have aTRH, we further restricted the population for the current analysis to participants who were taking one or more class of antihypertensive medication at the baseline examination, leaving 524 participants for the primary analysis.[10] Among this group, there were 43 participants who met the criteria for aTRH at baseline. After excluding these participants, 481 participants were included in the secondary analysis on the association of nocturnal hypertension and nondipping BP at baseline with incident aTRH at examination 2 or 3. The study was approved by the institutional review board governing human subjects' research at Tougaloo College, Jackson State University and University of Mississippi Medical Center. The current analysis of deidentified data was approved by the institutional review board at the University of Alabama at Birmingham. All participants provided written informed consent.

2.2 | Data collection

Baseline data were collected during an in-home interview, clinic examination, and ABPM. During the in-home interview, trained staff administered questionnaires to collect self-reported information on sociodemographics, health behaviors, previously diagnosed comorbid conditions, snoring and breathing cessation during sleep, and daytime tiredness. During the clinic examination, trained technicians measured height, weight, and BP; collected blood and urine samples; and recorded the names of prescription and over-the-counter medications taken in the 2 weeks before the study visit. Participants were asked to avoid caffeine, eating, heavy physical activity, and smoking and alcohol intake for 12 hours before the visit. After the baseline clinical examination, participants were invited to complete ABPM.

Using a modified Baecke questionnaire, the duration, frequency, and intensity of physical activity during active living, work, home life, and sport were recorded and summed to calculate a total physical activity score.[11] Higher scores represent more daily physical activity. Using weight and height as measured in the clinic visit, body mass index was calculated. Obesity was defined as a body mass index ≥ 30 kg/m^2. Sleep apnea risk was determined using available components that comprise the STOP-Bang screening tool.[12] Current smoking was defined by affirmative responses to the questions "Have you smoked more than 400 cigarettes in your lifetime?" and "Do you now smoke cigarettes?" Diabetes mellitus was defined as a fasting (≥8 hours) serum glucose ≥126 mg/dL, glycated hemoglobin ≥ .5%, or use of insulin or oral hypoglycemic medications within 2 weeks before the clinic examination. History of CVD was defined as self-reported myocardial infarction or stroke. Using serum creatinine collected during the baseline study visit, estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[13] Reduced estimated glomerular filtration rate was defined as < 60 mL/min per 1.73 m^2. Urinary albumin and creatinine were quantified from a 24-hour urine collection or from a spot urine sample using the nephelometric immunoassay and enzymatic methods, respectively.[14] Albuminuria was defined as a urinary albumin to urinary creatinine ratio ≥ 30 mg/g. Chronic kidney disease was defined by the presence of reduced estimated glomerular filtration rate or albuminuria. Antihypertensive medications were categorized by class, and the number of classes being taken by each participant was calculated.

2.3 | Clinic BP measurement

At each visit (examinations 1–3), clinic-measured BP was obtained following a standardized protocol.[9,15] After participants sat for at least 5 minutes in an upright position with their back and arms supported, feet flat on the floor and legs uncrossed, trained personnel measured BP two times for each participant on their right arm. One minute elapsed between the measurements. An appropriate cuff size, determined from an arm circumference measurement, was used.[9,15] The JHS Coordinating Center conducted routine training and retraining of technicians who measured BP. Quality control was assessed by monitoring digit preference for each technician and by comparing mean BP measurements within and between trained technicians. The two clinic-measured BP measurements were averaged for analysis.

A random-zero sphygmomanometer (Hawksley and Sons Ltd.) was used at the baseline examination (examination 1) and examination 2 and a semiautomatic oscillometric device (Omron HEM-907XL, Omron Healthcare Inc.) was used at examinations 2 and 3. Of the 4182 participants who attended examination 2, there were 2115 participants who had BP measured simultaneously with a random-zero sphygmomanometer and semiautomated oscillometric device using a Y-connector. In

TABLE 1 Baseline characteristics of Jackson Heart Study participants overall and by apparent treatment-resistant hypertension status

	Overall	Apparent treatment-resistant hypertension		
	N = 524	No n = 481	Yes n = 43	*P* value
Age, y	61.9 ± 9.2	61.6 ± 9.2	65.0 ± 8.8	.023
Male, %	25.8	24.9	34.9	.154
Physical activity score,[a] exercise units	8.2 ± 2.6	8.2 ± 2.7	7.5 ± 2.2	.094
Obese, %	56.7	56.3	60.5	.601
High obstructive sleep apnea risk,[b] %	80.9	80.0	90.7	.088
Current smoking, %	7.0	7.4	2.4	.219
Diabetes mellitus, %	33.1	31.3	53.5	.003
History of cardiovascular disease, %	12.2	10.4	32.6	<.001
Chronic kidney disease, %	19.5	18.6	29.4	.127
Mean clinic SBP, mm Hg	129.3 ± 14.7	128.0 ± 13.9	143.1 ± 16.6	<.001
Mean clinic DBP, mm Hg	74.2 ± 8.3	73.8 ± 8.0	78.6 ± 10.2	<.001
Uncontrolled clinic BP, %	21.4	17.0	69.8	<.001
Daytime SBP, mm Hg	130.4 ± 13.2	130.0 ± 13.1	135.6 ± 13.0	.007
Daytime DBP, mm Hg	77.4 ± 9.2	77.4 ± 9.2	77.3 ± 10.1	.936
Nocturnal SBP, mm Hg	122.7 ± 13.3	121.7 ± 13.1	133.3 ± 13.0	<.001
Nocturnal DBP, mm Hg	68.2 ± 8.7	68.0 ± 8.6	70.9 ± 9.5	.056
24-h SBP, mm Hg	127.7 ± 15.4	127.0 ± 15.1	135.8 ± 15.0	<.001
24-h DBP, mm Hg	73.8 ± 9.5	73.7 ± 9.4	75.1 ± 9.8	.377
Mean nighttime to daytime SBP ratio	0.938 ± 0.083	0.938 ± 0.081	0.986 ± 0.093	<.001
Antihypertensive medication classes,[c] %				
Diuretics	65.5	63.2	90.7	<.001
β-Blockers	22.3	18.7	62.8	<.001
Calcium channel blockers	36.6	33.1	76.7	<.001
Angiotensin-converting enzyme inhibitors	37.4	35.3	60.5	.001
Angiotensin receptor blockers	12.6	12.1	18.6	.215
Aldosterone receptor antagonists	1.7	1.5	4.7	.122
α_1-Antagonists	6.5	5.0	23.3	.001
α_2-Agonists and other centrally acting agents	5.9	4.0	27.9	<.001
Vasodilators	0.2	0.2	0.0	.918
Mean number of antihypertensive medication classes[c] %	1.9 ± 0.9	1.7 ± 0.7	3.6 ± 0.7	<.001

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure.
Values are expressed as percentages or mean ± standard deviation.
Nighttime to daytime systolic blood pressure (SBP) ratio was calculated as the nighttime SBP divided by daytime SBP.
[a]Higher score represents more daily physical activity.
[b]Obstructive sleep apnea risk score was estimated using the STOP-Bang screening tool. Scores ≥3 indicate high risk for sleep apnea.
[c]All participants included in the analysis were taking one or more class of antihypertensive medication.

these participants, robust regression was used to develop a model to calibrate the random-zero to the semiautomated clinic-measured BP as previously described.[16] When available, we used BP measured by the semiautomatic oscillometric device. Calibrated BP was used for all participants at examination 1 and for participants at examination 2 who only had their BP measured with the random-zero sphygmomanometer.

At each examination, controlled clinic-measured BP was defined as mean SBP/DBP < 140/90 mm Hg. aTRH was defined as clinic-measured SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg among participants taking three or more classes of antihypertensive medication or taking four or more antihypertensive medication classes regardless of BP level.

2.4 | Ambulatory BP monitoring

Following the baseline examination, participants were fitted with a Spacelabs 90 207 ABPM device on their nondominant arm. BP was recorded every 20 minutes for 24 hours. Using the IDACO criteria, participants were considered to have a complete ABPM if they had ≥10

TABLE 2 Prevalence ratios for nocturnal hypertension at baseline among Jackson Heart Study participants (n = 524)

	Prevalence of nocturnal hypertension, %	Prevalence ratio (95% confidence interval)		
		Model 1	Model 2	Model 3
Apparent treatment-resistant hypertension				
No	57.8	1 (reference)	1 (reference)	1 (reference)
Yes	83.7	1.38 (1.18–1.61)	1.33 (1.13–1.56)	1.20 (1.03–1.39)
Uncontrolled clinic BP				
No (SBP/DBP < 140/90 mm Hg)	52.4	1 (reference)	1 (reference)	1 (reference)
Yes (SBP/DBP ≥ 140/90 mm Hg)	87.5	1.62 (1.43–1.82)	1.63 (1.45–1.84)	1.24 (1.09–1.40)
No. of antihypertensive medication classes				
1	61.5	1 (reference)	1 (reference)	1 (reference)
2	54.8	0.91 (0.77–1.06)	0.91 (0.77–1.07)	1.02 (0.88–1.18)
3	61.6	0.98 (0.81–1.19)	0.95 (0.78–1.15)	0.99 (0.83–1.19)
4+	90.9	1.46 (1.23–1.74)	1.39 (1.14–1.70)	1.29 (1.06–1.56)
Antihypertensive medication classes				
Diuretics	54.2	0.81 (0.71–0.93)	0.83 (0.72–0.94)	0.91 (0.80–1.03)
β-Blockers	57.3	0.96 (0.81–1.14)	0.96 (0.81–1.14)	1.04 (0.89–1.22)
Calcium channel blockers	68.8	1.15 (1.01–1.32)	1.15 (1.01–1.32)	1.06 (0.94–1.20)
Angiotensin-converting enzyme inhibitors	63.3	1.06 (0.92–1.22)	1.01 (0.87–1.17)	1.08 (0.94–1.23)
Angiotensin receptor blockers	50.0	0.94 (0.73–1.21)	0.89 (0.69–1.14)	0.83 (0.66–1.05)
α_1-Antagonists	82.4	1.25 (1.04–1.51)	1.27 (1.04–1.53)	1.25 (1.03–1.52)
α_2-Agonists and other central-acting agents	90.3	1.57 (1.35–1.82)	1.48 (1.26–1.74)	1.27 (1.09–1.47)

Clinic blood pressure (BP) control: clinic-measured BP was defined as mean systolic BP (SBP)/diastolic blood pressure (DBP) <140/90 mm Hg.
Apparent treatment-resistant hypertension: clinic-measured SBP ≥140 mm Hg and/or DBP ≥90 mm Hg among participants taking three or more classes of antihypertensive medication or taking four or more antihypertensive medication classes with controlled clinic BP.
Model 1: adjustment for age and sex.
Model 2: adjustment for age, sex, obesity, obstructive sleep apnea risk, physical activity score, current smoking status, diabetes mellitus status, chronic kidney disease status, and history of cardiovascular disease status.
Model 3: adjustment for the variables in model 2 and daytime systolic and diastolic BP.

daytime (10 AM to 8 PM) and five or more nighttime (midnight to 6 AM) SBP and DBP measurements.[10] Nocturnal hypertension was defined by a mean SBP ≥ 120 mm Hg or mean DBP ≥ 70 mm Hg based on measurements between midnight and 6 AM.[3] The nighttime to daytime SBP ratio was calculated as the mean nighttime SBP divided by mean daytime SBP. Nondipping BP was defined as nighttime to daytime SBP ratio >0.9.

2.5 | Statistical analysis

Baseline characteristics and the prevalence of nocturnal hypertension and nondipping BP were calculated overall and by prevalent aTRH status at examination 1. Prevalence ratios (PRs; 95% confidence intervals [CIs]) for nocturnal hypertension and nondipping BP associated with aTRH, controlled clinic-measured BP, number of antihypertensive medication classes being taken, and individual antihypertensive medication classes were calculated using modified Poisson regression with robust standard errors. Variables measured at baseline were used to adjust for potential confounding in three nested regression models. Model 1 adjusted for age and sex, model 2 included additional adjustment for obesity, obstructive sleep apnea risk, physical activity score, current smoking status, diabetes mellitus status, chronic kidney disease status, and history of cardiovascular disease. Model 3 included adjustment for daytime SBP and

TABLE 3 Prevalence ratios for nondipping nocturnal BP at baseline among Jackson Heart Study participants

	Prevalence of nondipping nocturnal BP, %	Prevalence ratio (95% confidence interval)		
		Model 1	Model 2	Model 3
Apparent treatment-resistant hypertension				
No	66.1	1 (reference)	1 (reference)	1 (reference)
Yes	88.4	1.31 (1.15–1.48)	1.29 (1.12–1.47)	1.25 (1.09–1.43)
Uncontrolled clinic BP				
No (SBP/DBP < 140/90 mm Hg)	65.8	1 (reference)	1 (reference)	1 (reference)
Yes (SBP/DBP ≥ 140/90 mm Hg)	75.9	1.12 (0.99–1.28)	1.13 (0.99–1.28)	1.07 (0.93–1.22)
No. of antihypertensive medication classes				
1	67.7	1 (reference)	1 (reference)	1 (reference)
2	65.6	0.97 (0.85–1.11)	0.97 (0.84–1.11)	0.98 (0.86–1.13)
3	68.6	1.01 (0.85–1.20)	0.98 (0.82–1.17)	0.99 (0.83–1.18)
4+	90.9	1.33 (1.13–1.56)	1.29 (1.09–1.52)	1.24 (1.05–1.47)
Antihypertensive medication classes				
Diuretics	64.1	0.87 (0.78–0.98)	0.86 (0.77–0.97)	0.88 (0.78–0.99)
β-Blockers	72.6	1.10 (0.97–1.26)	1.11 (0.97–1.27)	1.12 (0.98–1.29)
Calcium channel blockers	70.8	1.03 (0.92–1.16)	1.03 (0.92–1.16)	1.01 (0.90–1.14)
Angiotensin-converting enzyme inhibitors	72.4	1.11 (0.98–1.26)	1.09 (0.96–1.24)	1.09 (0.96–1.24)
Angiotensin receptor blockers	56.1	0.89 (0.71–1.12)	0.88 (0.70–1.10)	0.88 (0.70–1.10)
α_1-Antagonists	88.2	1.30 (1.11–1.51)	1.29 (1.10–1.51)	1.27 (1.09–1.49)
α_2-Agonists and other centrally acting agents	83.9	1.24 (1.05–1.47)	1.21 (1.02–1.43)	1.17 (0.98–1.38)

Clinic blood pressure (BP) control: clinic-measured BP was defined as mean systolic BP (SBP)/diastolic BP (DBP) <140/90 mm Hg.
Apparent treatment-resistant hypertension: clinic-measured SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg among participants taking three or more classes of antihypertensive medication or taking four or more antihypertensive medication classes with controlled clinic BP.
Model 1: adjustment for age (per 10 years higher) and sex.
Model 2: adjustment for the variables in model 1 plus obesity, obstructive sleep apnea risk, physical activity score, current smoking status, diabetes mellitus status, chronic kidney disease status, and history of cardiovascular disease status.
Model 3: adjustment for the variables in model 2 plus obesity, obstructive sleep apnea risk, physical activity score, current smoking status, diabetes mellitus status, chronic kidney disease status, history of cardiovascular disease status, and 24-hour systolic and diastolic BP.

DBP when nocturnal hypertension was the outcome and 24-hour SBP and DBP when nondipping SBP was the outcome. Next, after excluding participants with prevalent aTRH at the baseline examination, the percentage of participants who developed incident aTRH at examinations 2 and 3 was calculated for those with and without nocturnal hypertension and, separately, with and without nondipping BP. As the exact time that incident aTRH developed was not known, only that it was between examination visits, hazard ratios for incident aTRH associated with nocturnal hypertension and nondipping BP were calculated using interval-censored Cox regression. Five models with progressive adjustment for baseline variables were estimated. Model 1 included adjustment for age and sex. Model 2 included adjustment for age, sex, obesity, obstructive sleep apnea risk, physical activity score, current smoking, diabetes mellitus, chronic kidney disease, and history of CVD. Model 3 included adjustment for the variables in model 2 and diuretic use and number of antihypertensive medication classes being taken. Model 4 included the variables in model 3 plus baseline clinic SBP and DBP. Model 5 adjusted for variables in model 4 plus daytime SBP and DBP when nocturnal hypertension was the primary exposure and 24-hour SBP

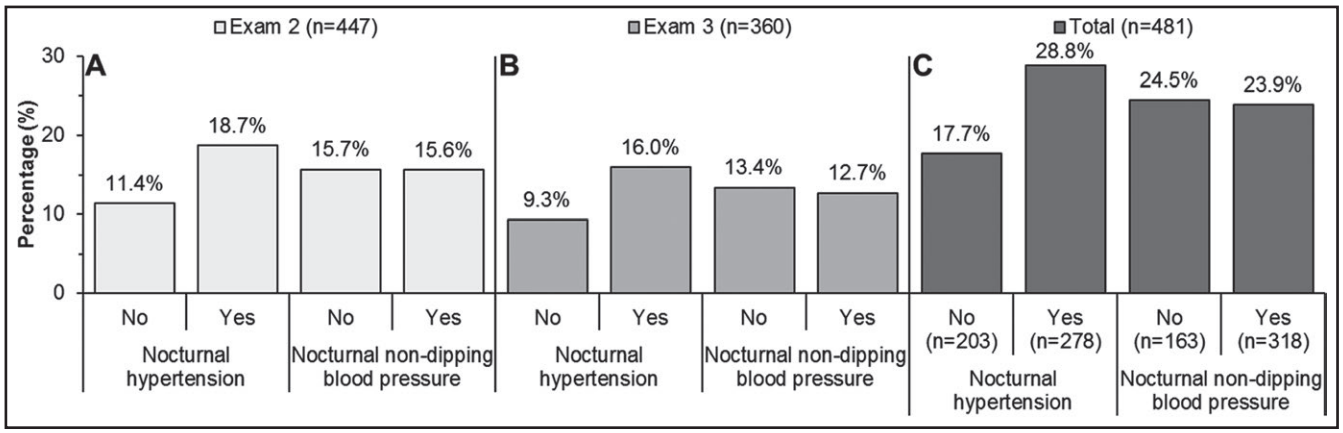

FIGURE Proportion of Jackson Heart Study participants with and without nocturnal hypertension and nondipping nocturnal blood pressure who developed apparent treatment-resistant hypertension. A, Examination 2 incident apparent treatment-resistant hypertension; B, Examination 3 incident apparent treatment-resistant hypertension; C, Total incident apparent treatment-resistant hypertension across examinations 2 and 3.

and DBP when nondipping SBP was the primary exposure. Analyses were conducted using SAS version 9.4 (SAS Institute Inc).

3 | RESULTS

3.1 | Participant characteristics

Among the 524 participants in the current analysis, the prevalence of aTRH was 8.2%. Overall, the mean ± standard deviation (SD) age was 61.9 ± 9.2 years and 25.8% of participants were men (Table 1). The mean ± SD nighttime SBP and DBP were 122.7 ± 13.3 and 68.2 ± 8.7, respectively. The mean nighttime to daytime SBP ratio was 0.938 ± 0.083. Participants with aTRH were older, more likely male, more likely to have a higher prevalence of diabetes mellitus, and more likely to have a history of CVD than their counterparts without aTRH. Clinic and nocturnal SBP and DBP values were higher and the nighttime to daytime SBP ratio was larger among participants with vs those without aTRH. On average, participants with aTRH were taking 3.6 ± 0.7 classes of antihypertensive medications compared with 1.7 ± 0.7 classes for participants without aTRH. Among those with aTRH, there was high concordance (91%) of BP control defined in the clinic and on ABPM. No participants with aTRH had uncontrolled clinic BP and controlled 24-hour BP (SBP/DBP <130/80 mm Hg), while only four participants had controlled

TABLE 4 Hazard ratios for incident apparent treatment-resistant hypertension associated with nocturnal hypertension and nocturnal nondipping BP among Jackson Heart Study participants

Hypertension status	Cases at risk, No. (%)	Hazard ratio (95% confidence interval)				
		Model 1	Model 2	Model 3	Model 4	Model 5
Nocturnal hypertension						
No	36/203 (17.7)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Yes	80/278 (28.8)	1.96 (1.33–2.76)	1.79 (1.24–2.58)	1.63 (1.10–2.42)	1.45 (0.96–2.17)	1.21 (0.77–1.87)
Nondipping BP						
No	40/163 (24.5)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Yes	76/318 (23.9)	1.14 (0.80–1.63)	1.06 (0.74–1.53)	0.95 (0.65–1.40)	0.94 (0.64–1.38)	0.94 (0.64–1.38)

Model 1: Adjustment for age and sex.
Model 2: adjustment for age, sex, obesity, obstructive sleep apnea risk, physical activity score, current smoking status, diabetes mellitus status, chronic kidney disease status, and history of cardiovascular disease status.
Model 3: adjustment for the variables in model 2 and status of baseline diuretic use and number of antihypertensive medication classes.
Model 4: adjustment for the variables in model 3 and clinic systolic and diastolic blood pressure (BP).
Model 5: adjustment for the variables in model 4 and daytime systolic and diastolic BP for the analyses with nocturnal hypertension at baseline as the exposure of interest and 24-hour systolic and diastolic BP for the analyses with nondipping BP at baseline as the exposure of interest.

clinic BP but uncontrolled 24-hour BP (SBP ≥ 30 mm Hg and/or DBP ≥ 80 mm Hg).

3.2 | Nocturnal hypertension among participants with aTRH

At baseline, 83.7% and 57.8% of participants with and without aTRH, respectively, had nocturnal hypertension. After multivariable adjustment, aTRH was associated with a 1.20 (95% CI, 1.03–1.39) times higher prevalence of nocturnal hypertension (Table 2). The prevalence of nocturnal hypertension was 52.4% and 87.5% for participants with and without controlled clinic BP, respectively. The full multivariable-adjusted PR for nocturnal hypertension comparing participants with uncontrolled clinic BP with those with controlled clinic BP was 1.24 (95% CI, 1.09–1.40). Treatment with four or more medication classes was associated with a higher prevalence of nocturnal hypertension, before and after multivariable adjustment. Treatment with an α_1-antagonist was associated with a higher prevalence of nocturnal hypertension (multivariable-adjusted PR, 1.25; 95% CI, 1.03–1.52). In addition, α_2-agonists and other centrally acting agents were associated with a higher prevalence of nocturnal hypertension (multivariable-adjusted PR, 1.27; 95% CI, 1.09–1.47).

3.3 | Nondipping BP among participants with aTRH

Overall, 88.4% and 66.1% of participants with and without aTRH, respectively, had nondipping BP at baseline (Table 3). aTRH, taking four or more compared with one class of antihypertensive medication, and taking an α_1-antagonist were each associated with a higher multivariable-adjusted PR for nondipping BP. Taking a diuretic was associated with a lower multivariable-adjusted PR for nondipping BP.

3.4 | Nocturnal hypertension, nondipping BP, and incident aTRH

During a median (25th–75th percentile) follow-up of 7.3 (5.0–8.1) years, 115 of 481 participants (23.9%) developed aTRH. Among participants with nocturnal hypertension at baseline, 28.8% developed aTRH compared with 17.7% of participants without nocturnal hypertension (Figure). Overall, 23.9% and 24.5% of participants with and without nondipping BP, respectively, at baseline developed aTRH. Nocturnal hypertension was associated with developing aTRH after adjustment for age, sex, obesity, obstructive sleep apnea risk, physical activity score, current smoking status, diabetes mellitus, chronic kidney disease, history of cardiovascular disease, diuretic use, and number of antihypertensive medication classes being taken at baseline (Table 4; top panel, models 1 through 3). This association was no longer statistically significant after further adjustment. Nondipping BP was not associated with developing aTRH during follow-up, before or after multivariable adjustment (Table 4; bottom panel).

4 | DISCUSSION

In the current study of black patients who were treated for hypertension, aTRH was associated with a higher prevalence of nocturnal hypertension and nondipping BP. Also, participants with uncontrolled clinic BP had a higher prevalence of nocturnal hypertension. Participants taking a diuretic were less likely to have nondipping BP. Meanwhile, participants taking an α_2-agonist or other centrally acting agent were more likely to have nocturnal hypertension, and α_1-antagonist use was associated with a higher prevalence of both nocturnal hypertension and nondipping. Among participants without prevalent aTRH, nocturnal hypertension was associated with developing aTRH, but this association was no longer present after adjustment for baseline levels of clinic or mean daytime SBP and DBP. Nondipping BP was not associated with developing aTRH.

Prior studies indicate that blacks have a high prevalence of nocturnal hypertension and nondipping BP. In the CARDIA (Coronary Artery Risk Development in Young Adults) study,[17] blacks were markedly more likely than whites to have nocturnal hypertension (PR, 2.44; 95% CI, 0.99–6.05) and nondipping BP (PR, 2.50; 95% CI, 1.39–4.48). In a study that aimed to characterize nocturnal BP among blacks (N = 62) and whites (N = 72) with hypertension taking antihypertensive medication whose daytime BP values were comparable, the prevalence of nondipping SBP and DBP was 63% and 45%, respectively, among blacks and 47% and 28%, respectively, among whites.[18] The authors concluded that the higher nocturnal BP in blacks compared with whites could contribute to their higher incidence of target organ damage.[18]

Prior studies have reported that black race, older age, female sex, sodium sensitivity, sleep apnea, socioeconomic status, and psychosocial factors (eg, depressive symptoms) are associated with nondipping BP.[19] A previous analysis of JHS data reported perceived social support to be associated with a lower prevalence of nondipping BP.[20] In another JHS report, a more active social network was associated with a lower prevalence of aTRH.[21] In the current study, uncontrolled clinic BP was associated with a higher prevalence of nocturnal hypertension; however, potentially more important was that > 50% of participants with controlled clinic BP had nocturnal hypertension, highlighting the usefulness of ABPM to identify individuals with this high-risk phenotype. Having more severe hypertension requiring treatment with four or more vs one class of antihypertensive medication was associated with a higher prevalence of nocturnal hypertension and nondipping BP. Also, having aTRH was associated with a higher prevalence of nocturnal hypertension and nondipping. A study from the Spanish ABPM registry (n = 5128) also suggested that nighttime SBP and DBP is high (SBP: 136 ± 17 mm Hg and DBP: 81 ± 11 mm Hg) and nondipping BP is common (64.8%) among individuals with aTRH confirmed by ABPM (24-hour SBP ≥ 130 and/or DBP ≥ 80 mm Hg).[22] Given the high prevalence of nocturnal hypertension and nondipping BP among individuals with aTRH, treatment strategies directed at lowering nighttime BP and increasing BP dipping may be warranted. One prior randomized trial suggests that taking antihypertensive medication at bedtime may lower nighttime SBP to a greater extent than taking it in the morning.[23] Renal denervation is another treatment strategy that could benefit

patients with treatment-resistant hypertension and an altered nighttime BP profile. However, results from the SYMPLICITY HTN-3 trial[24] suggested that renal denervation only marginally improved nighttime SBP levels in a population with treatment-resistant hypertension taking an average of five classes of antihypertensive medications (−6.1 ± 18.2 mm Hg vs −1.6 ± 19.7 mm Hg for renal denervation vs sham control; P = .02).

Diuretic treatment was associated with a lower prevalence of nondipping BP in the current study. This result supports the hypothesis that pressure natriuresis may play a role in nondipping where BP remains high during sleeping hours to counteract sodium retention during the day.[25] Several small crossover studies comparing diurnal BP patterns in Japanese participants on a high-sodium compared with a low-sodium diet suggest that a low-sodium diet may restore a dipping pattern in salt-sensitive individuals with hypertension.[26–29] Diuretics, which block the renal sodium chloride transporter, may reproduce the effect of dietary restriction on sodium balance as they are effective treatments among patients with nondipping BP.[30,31] Diuretics may be especially beneficial in blacks, a population with a high prevalence of salt-sensitive hypertension.[28] Overall, the current results support the importance of diuretics as a component of antihypertensive treatment among blacks and for patients with aTRH.

α_1-Antagonist use was associated with both nocturnal hypertension and nondipping BP, while participants taking α_2-agonists and other centrally acting agents had a higher prevalence of nocturnal hypertension. Angiotensin receptor blockers and angiotensin-converting enzyme inhibitors target the renin-angiotensin-aldosterone system (RAAS), which is activated during sleep and may increase BP, but neither medication class was protective for nocturnal hypertension or nondipping in this study. In the Spanish ABPM registry, monotherapy with nondihydropyridine calcium channel blockers and α_1-antagonists were both associated with less nocturnal BP decline compared with other antihypertensive drug classes.[32] Consistent with these data, α_1-antagonist use was associated with a 1.25- and 1.27-fold higher prevalence of nocturnal hypertension and nondipping, respectively, in the current study. One possible mechanism for this finding is the sodium reabsorption from the proximal tubule and the antinatriuresis caused by antagonism of α_1 adrenoreceptors.[33] This finding further supports the hypothesis that pressure natriuresis plays a role in nondipping BP. Additionally, calcium channel blocker use was associated with nocturnal hypertension after adjusting for clinical variables and clinic-measured BP level, but the association was attenuated after adjustment for mean daytime SBP and DBP from ABPM. Overall, these results suggest that α_1-antagonists and α_2-agonists plus other centrally acting agents should be evaluated further for the treatment of an elevated nighttime BP profile in this race group. [34]

Over 15 years of follow-up in the CARDIA study, participants with vs those without nondipping BP were more likely to transition from normal BP (SBP/DBP < 120/80 mm Hg) to prehypertension and from prehypertension to hypertension.[6] However, this association was not statistically significant after adjustment for demographic factors, CVD risk factors, comorbidities, and baseline clinic BP level. The current study suggests that neither nocturnal hypertension nor nondipping BP is associated with risk for developing aTRH after taking into account daytime BP levels. These results indicate that a higher nighttime BP profile may not be a risk factor for worsening clinic-measured BP in treated black patients independent of daytime BP.

5 | STUDY STRENGTHS AND LIMITATIONS

This study has several strengths. The JHS is a community-based, longitudinal study comprised exclusively of blacks with prospective observational data collected on clinic BP and antihypertensive treatment. Also, the JHS is one of the largest community-based studies to have conducted 24-hour ABPM in blacks. A standardized protocol was used to collect information on hypertension and CVD risk including risk factors for hypertension and CVD, clinic-measured BP, antihypertensive medication by pill bottle review, and ABPM. The current study has several limitations. Repeated ABPM measurements were not available to evaluate reproducibility or the association of baseline aTRH with the incidence of nocturnal hypertension and nondipping BP during follow-up. During the pill bottle review, a pill count was not performed to provide an objective measure of medication adherence. Additionally, some studies suggest that the timing of administration of antihypertensive medication (ie, morning or evening) may relate to the risk of nocturnal hypertension and nondipping BP, but this information was not available in JHS.

6 | CONCLUSIONS

The results from the current study confirm that nocturnal hypertension and nondipping BP are common among black patients. Nocturnal hypertension and nondipping BP were each more common among participants with vs those without aTRH. No antihypertensive medication class was protective for nocturnal hypertension, while diuretics were the only class protective for nondipping BP. α_1-Antagonist use was associated with both nocturnal hypertension and nondipping BP, while α_2-agonists were associated with nocturnal hypertension. Nocturnal hypertension and nondipping were not associated with developing aTRH after adjustment for clinic or daytime BP. Overall, our study highlights the need for treatment strategies directed towards blacks to reduce aTRH, nocturnal hypertension, and nondipping BP.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

ORCID

Marguerite R. Irvin http://orcid.org/0000-0002-1442-2023

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